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Clinical Communications

mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase

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Clinical Implications

mRNA COVID-19 vaccines that contain polyethylene glycol (PEG) can be safely administered in oncology patients with immediate hypersensitivity reactions to pegaspargase and PEG3350 tolerance.

Pegaspargase is a vital component of a multidrug chemotherapy regimen for treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). Pegaspargase is manufactured by chemically conjugating *Escherichia coli*—derived L-asparaginase with polyethylene glycol (PEG5000).[1] By itself, *E. coli*—derived L-asparaginase is associated with high rates of hypersensitivity reactions.[1] The pegylated form has extended half-life and improved immunogenicity profile compared with the native form, resulting in lower rates of hypersensitivity reactions.[1,2] Tolerance of pegaspargase after a hypersensitivity reaction to *E. coli*—derived L-asparaginase suggests different antigenic sites.[1] However, pegaspargase is also commonly associated with immediate hypersensitivity reactions, with incidence ranging from 3% to 41%.[3] Infusion reactions to pegaspargase might therefore be due to PEG given the presence of anti-PEG antibodies in several studies, but may also be due to reactivity against asparaginase itself. Reactions to pegaspargase are of an immediate hypersensitivity phenotype, but the class of PEG-specific antibodies detected in these patients has previously been reported as primarily IgG, not IgE.[4] IgE-mediated PEG allergy is rare but has been demonstrated with positive skin testing and elevated specific IgE levels.[5-7] Interestingly, patients with immediate hypersensitivity to pegaspargase typically have subsequent tolerance to PEG3350, which is routinely used to treat constipation associated with other chemotherapeutic agents for ALL and LL. However, patients and clinicians maintain high vigilance toward the possibility of cross-reactivity reactions to higher-molecular-weight PEG-containing products.

During the rollout of COVID-19 mRNA vaccines in the United Kingdom, Europe, and the United States in December 2020, a great deal of attention was directed toward considering an association between immediate hypersensitivity reactions to the vaccines and PEG2000, a stabilizing component of the lipid nanoparticle carrier molecule for the mRNA spike protein construct in the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines that had not been a component of any prior licensed vaccine. Currently, there are no recommendations on how to evaluate the safety of mRNA COVID-19 vaccines in those who report an immediate hypersensitivity reaction to pegaspargase. We therefore sought to understand the safety of PEG2000-containing mRNA COVID vaccines in patients who reported a label of immediate pegaspargase hypersensitivity.

We present a prospective case series of 19 patients who were candidates for the mRNA COVID-19 vaccine but had a history of immediate hypersensitivity reactions to pegaspargase evaluated at outpatient drug allergy clinics at Vanderbilt University Medical Center (VUMC) and Texas Children's Hospital (TCH) between April 2021 and July 2021. This study was performed under institutional review board (IRB) approved protocols from Vanderbilt University IRB #161455. After careful evaluation of the index reaction history, each patient at VUMC underwent a standard skin testing protocol containing PEG3350 (skin prick only 1.7 and 17 mg/mL), PEG8000 (skin prick only 0.1 and 1 mg/mL), and methylprednisolone acetate (skin prick and intradermal 4 and 0.4 mg/mL), which contains PEG3350, as the primary agents of interest. In patients with negative skin testing at VUMC, a direct challenge with Pfizer-BioNTech mRNA COVID-19 vaccine 0.5 mL was administered undiluted intramuscularly followed by a 1-hour observation to monitor for any immediate reaction. At TCH, patients who reported a history of tolerance to PEG3350 were given the option to receive the Pfizer-BioNTech mRNA COVID-19 vaccine followed by a 30-minute observation, without prior skin testing. Those who did not report a history of tolerance to PEG3350 or who preferred to receive skin testing underwent a previously reported skin testing protocol before recommendation of the vaccine.[8]

The demographics, index reaction history, and testing results of the 19 patients are summarized in Table I. Of the patients evaluated with the protocol above, 9 (47.4%) were female and the average age was 16.5 years (range: 12-33 years). An average of 6.6 years (range: 1-20 years) had passed since their index pegaspargase reaction. Apart from 1 patient, the reactions were all immediate phenotype, with the typical onset of symptoms within 1 to 60 minutes of drug receipt. Of the 19 patients, 15 (78.9%) experienced a reaction with the first or second dose of pegaspargase. The patients had varying levels of symptom severity, but 18 reactions involved 2 or more systems. Treatment also varied from antihistamine alone to 8 of 19 (42.1%) of the patients receiving epinephrine. Of the 19 patients, 16 (84.2%) reported having tolerated PEG3350 subsequent to their reaction to pegaspargase.

Of the 19 patients, 14 had negative skin testing before immunization and the remaining 5 patients who had tolerated PEG3350 went on to immunization without skin testing. All 19 patients tolerated their first dose of Pfizer-BioNTech SARS-CoV-2 vaccine with no symptoms. Subsequently, the patients were given the option to receive their second doses in the regular vaccination centers with 30-minute observation, and all 19 patients tolerated their second doses uneventfully.

Because of the presence of PEG2000 in the mRNA COVID-19 vaccines, it is important to investigate whether there is any potential immunological cross-reactivity in patients who have previously experienced hypersensitivity reactions to pegaspargase. This case series is the first to demonstrate that patients with immediate hypersensitivity reactions to pegaspargase appear to safely

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TABLE I. Patient demographics, pegaspargase reaction history, PEG skin testing, and mRNA COVID-19 challenge history

			Index reaction history					Testing visit	Vaccine dose 1 result		Vaccine dose 2 result
Center	Age (y)	Sex	Date of reaction	Signs and symptoms	Onset of symptoms (min)	Treatment received	Subsequent PEG exposure?	PEG skin testing result*	1-h observation outcome	24-h follow-up phone call	Postvaccination follow-up phone call
VUMC	13	F	2017 2nd dose	Difficulty breathing, facial flushing	10	Diphenhydramine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	13	M	2014 2nd dose	Erythema, flushing, shortness of breath	5	Diphenhydramine, hydrocortisone	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	17	F	2014 2nd dose	Shortness of breath, lip, and tongue swelling	10	Diphenhydramine, hydrocortisone, ranitidine, epinephrine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	13	M	2016 2nd dose	Rash, throat tightness, vomiting	5	Diphenhydramine, hydrocortisone	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	13	M	2016 1st dose	Shortness of breath, flushing, tongue swelling, tachycardia	20	Systemic steroid	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	13	M	2021 2nd dose	Facial erythema, facial swelling, shortness of breath, vomiting	30	Diphenhydramine, hydrocortisone, epinephrine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	33	F	2001 11th dose	Shortness of breath, unconsciousness	1	Epinephrine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	25	F	2011 2nd dose	Diffuse erythema, pruritus, hypotensive	2	Methylprednisolone, epinephrine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
VUMC	17	M	2018 1st dose	Facial and lip swelling, difficulty breathing, urticaria, emesis	2	Diphenhydramine, hydrocortisone	No	Negative	No symptoms	No symptoms	No symptoms
VUMC	14	F	2018 3rd dose	Diffuse urticaria, nausea, hypotension	15	Diphenhydramine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
TCH	16	F	2018 2nd dose	Facial flushing, periorbital edema, cough, emesis	3	Diphenhydramine, hydrocortisone	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
TCH	16	M	2007 2nd dose 2008 3rd dose	1st: Urticaria 2nd: Cough, shortness of breath, voice change, tongue swelling	1st: 12hrs 2nd: 24hrs	Diphenhydramine Diphenhydramine, epinephrine	Yes, Miralax	Negative	No symptoms	No symptoms	No symptoms
TCH	13	M	2013 4th dose	Urticaria, difficulty breathing, cough, wheezing	5	Diphenhydramine, hydrocortisone, epinephrine	No	Negative	No symptoms	No symptoms	No symptoms
TCH	12	M	2014 2nd dose	Facial and orbital erythema, upper lip swelling, tongue pruritus	5	Diphenhydramine, hydrocortisone	No	Negative	No symptoms	No symptoms	No symptoms

TCH	16	F	2013 1st dose 2014 2nd dose	Erythema, urticaria, pruritus, periorbital edema	15	Diphenhydramine	Yes, Miralax	Not done†	No symptoms	No symptoms	No symptoms
TCH	17	M	2016 3rd dose	Pruritus, coughing, facial erythema	5	Diphenhydramine	Yes, Miralax	Not done†,‡	No symptoms	No symptoms	No symptoms
TCH	16	F	2015 2nd dose	Throat tightness, pruritus, vomiting	5	Diphenhydramine, methylprednisolone, ranitidine, epinephrine	Yes, Miralax	Not done†	No symptoms	No symptoms	No symptoms
TCH	21	M	2018 1st dose	Palpitations	60	Diphenhydramine, ranitidine	Yes, Miralax	Not done†,‡	No symptoms	No symptoms	No symptoms
TCH	16	F	2015 2nd dose	Throat tightness, pruritus, vomiting	5	Diphenhydramine, methylprednisolone, ranitidine, epinephrine	Yes, Miralax	Not done†	No symptoms	No symptoms	No symptoms

PEG, Polyethylene glycol; *TCH*, Texas Children's Hospital; *VUMC*, Vanderbilt University Medical Center.
*At VUMC, the PEG skin testing protocol included PEG3350 (skin prick only 1.7 and 17 mg/mL), PEG8000 (skin prick only 0.1 and 1 mg/mL), and methylprednisolone acetate (skin prick and intradermal 4 and 0.4 mg/mL). At TCH, the PEG skin testing protocol included PEG3350 (skin prick only 1.7, 17, and 170 mg/mL), and methylprednisolone acetate (skin prick 40 mg/mL and intradermal 4 and 0.4 mg/mL).
†PEG skin testing not performed because the patient had known tolerance of PEG3350.
‡PEG skin testing not performed because the patient had known tolerance of subsequent administration of pegaspargase.

tolerate the Pfizer-BioNTech mRNA COVID-19 vaccine. After an initial hypersensitivity reaction to pegaspargase, patients have a theoretical risk for reactions to other PEG-containing products due to the potential presence of long-lived PEG antibodies. If antibodies are of the IgE subclass, this could lead to an IgE-mediated immediate hypersensitivity reaction; if IgG or IgM subclasses, this could lead to complement activation—related pseudoallergy that can be easily confused with IgE-mediated reactions. However, the mechanism behind immediate hypersensitivity reactions to pegaspargase does not typically appear to be IgE-mediated.[4] In this case series, we provide further evidence that IgE-mediated sensitization to PEG is unlikely to be the primary mechanism for pegaspargase immediate hypersensitivity, as 2 patients reported subsequent tolerance to pegaspargase without symptoms, 16 patients reported consuming PEG3350 without any symptoms, and 14 patients had negative skin testing, including 10 patients with negative prick testing to the higher-molecular-weight PEG8000. The subsequent tolerance of pegaspargase in 2 cases highlights that the original reaction was either not related to pegaspargase or was related to a non—IgE-mediated mechanism; our report does not differentiate between these possibilities. Allergenicity of PEG reportedly increases as the density and molecular weight of PEG increases. Therefore, patients with IgE-mediated sensitization to PEG have been shown to lose sensitization to lower-molecular-weight PEG before higher-molecular-weight PEG and reactivity to lower-molecular-weight PEG can be variable.[5] The lack of evidence of any immediate reaction on either the first or second dose of the Pfizer-BioNTech COVID-19 mRNA vaccines also does not support an IgE mechanism or immunological resensitization to PEG as a result of immunization.

A limitation of our study is that we did not measure PEG IgE, IgM, or IgG before vaccination; however, these antibody tests are not commercially available and have yet to be validated across multiple populations in widespread studies. Serum tryptase levels were also not available for evaluation. Another limitation is that the majority of our patients experienced the pegaspargase hypersensitivity reactions >5 years before the evaluation for the mRNA COVID-19 vaccines; however, 9 of 19 (47%) patients were within 5 years of their original reaction. With lower expected age eligibility for the vaccine, it will be important to evaluate if our results hold for those with more recent pegaspargase reactions, who may still have IgM, IgG, or IgE PEG antibodies. This is also important because the clinical relevance of IgM and IgG, which is present at low levels in 5% to 9% of the population, is not clear. Whether these patients might ever demonstrate anti-PEG sIgE or positive PEG skin testing in the early pegaspargase reaction period remains unknown.

Beyond the ongoing mechanistic questions underlying pegasparagase reactions, we provide preliminary supportive evidence that patients with a previous immediate reaction to pegaspargase can be safely vaccinated with mRNA vaccines containing PEG2000. PEG skin testing was intentionally completed in all patients evaluated at VUMC as part of the research protocol and to determine the utility of skin testing before vaccine challenge, whether or not patients subsequently tolerated PEG-containing products after their index reaction. As demonstrated by the patients evaluated at TCH who did not undergo skin testing due to known prior tolerance of PEG3350, PEG skin testing is unlikely to be necessary in that circumstance before PEG-containing mRNA vaccines. In this population of patients with ALL in complete remission, our study was focused on COVID-19 vaccine

safety. The objective of our evaluation focused on determining whether patients with labels of immediate reactions to pegaspargase could safely receive mRNA vaccines containing PEG 2000. To our knowledge, PEG testing in pegaspargase reactors has not been reported previously. Because our focus was on COVID-19 vaccine safety, we did not perform skin testing or challenges with pegaspargase, and hence we acknowledge that we did not directly or specifically address the pegaspargase allergy that remains as a warning in the patient chart.

In summary, our case series of safe COVID-19 mRNA vaccination in ALL survivors with a history of immediate reactions to pegaspargase provides reassurance that this is a safe strategy. Although our study achieved the major aim of achieving safe vaccination in ALL survivors, it cannot comment on the pegaspargase allergy label or future safety of pegaspargase or other pegylated drugs. Our study remains further limited in its scope and generalizability by lack of inclusion of children under 12 and those with more recent reactions to pegaspargase who are not yet eligible for COVID-19 vaccination. Although our experience suggests that routine PEG skin testing and evaluations in similar patients are likely to be low yield and may serve only to delay COVID-19 vaccination, select higher risk patients with recent anaphylaxis or patients where fear of the previous pegaspargase reaction acts as a barrier to vaccination may still benefit from specialty allergy assessment or skin testing and observed vaccination.

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Conflicts of interest: E. J. Phillips receives royalties from UpToDate and consulting fees from Janssen, Vertex, Biocryst, and Regeneron. She is co-director of IIID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. Funders played no role in any aspect of this manuscript. The rest of the authors declare that they have no relevant conflicts of interest.

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